

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

17-970/S-046

Pharmacology Review(s)

Division of Oncology Drug Products, HFD-150
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Review for Labeling Update

NDA: 17,970

Reviewer: Margaret Brower, Ph.D.

Date Review Completed: June 14, 2000

Sponsor: Zeneca Pharmaceuticals

Drug:

Generic name: Tamoxifen

Trade name: Nolvadex

Indication: breast cancer

Route of administration and dosage form: oral tablet

Recommended dosage and schedule: 20-40mg/day for up to 5y

Studies reviewed for this submission:

Kivisto, K., et al. 1998. Tamoxifen and toremifene concentrations in plasma are greatly decreased by rifampin. *Clinical Pharm. & Therapeutics* 64(6): 648.

Hemminki, K., et al. 1995. DNA adducts caused by tamoxifen and toremifene in human microsomal system and lymphocytes in vitro. *Carcinogenesis*, 16(7): 1661.

Hard, G., et al. 1993. Major differences in the hepatocarcinogenicity and DNA adduct forming between toremifene and tamoxifen in female Crl:CD(BR) rats. *Cancer Res.* 53:4534.

Williams, G., et al. 1993. The triphenylethylene drug tamoxifen is a strong liver carcinogen in the rat. *Carcinogenesis*, 14(2): 315.

Moorthy, B., et al. 1996. Tamoxifen metabolic activation: comparison of DNA adducts formed by microsomal and chemical activation of tamoxifen and 4-hydroxytamoxifen with DNA adducts formed *in vivo*. *Cancer Res.* 56:53.

White, I., et al. 1992. Genotoxic potential of tamoxifen and analogues in female Fischer F344/n rats, DBA/2 and C57BL/6 mice and in human MCL-5 cells. *Carcinogenesis*. 13(12): 2197.

Supplemental review of chronic toxicity in rodents administered tamoxifen. NDA 17,970. M.Brower. April, 1994.

The following changes should be included in the revised labeling.

1. **WARNINGS**

DRAFT

1 pages redacted from this section of
the approval package consisted of draft labeling

DRAFT

/S/**RECOMMENDATIONS**

The label should be corrected as indicated above.

/S/

Margaret E. Brower, Ph.D.
Pharmacology/Toxicology6/26/00
Date

cc.

NDA ORIG. and Div. File

HFD-150

/SHonig

/WSchmidt

/MBrower

/ABaird

/S/

6/27/00